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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/780,757 | 02/08/2001 | Ycchezkel Barenholz | BARENHOLZ=1 | 6619 |

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Browdy and Neimark
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Washington, DC 20001

EXAMINER

FREDMAN, JEFFREY NORMAN

ART UNIT PAPER NUMBER

1637

DATE MAILED: 12/22/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

| | | |
|-----------------|------------------|--|
| Application No. | Applicant(s) | |
| 09/780,757 | BARENHOLZ ET AL. | |
| Examiner | Art Unit | |
| Jeffrey Fredman | 1637 | |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) Responsive to communication(s) filed on 15 November 2004.

2a) This action is **FINAL**. 2b) This action is non-final.

3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4) Claim(s) 19-33 and 35-42 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5) Claim(s) 19-33 is/are allowed.

6) Claim(s) 35-42 is/are rejected.

7) Claim(s) _____ is/are objected to.

8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9) The specification is objected to by the Examiner.

10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.

12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) All b) Some * c) None of:
1. Certified copies of the priority documents have been received.
2. Certified copies of the priority documents have been received in Application No. _____.
3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.

15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) Notice of References Cited (PTO-892) 4) Interview Summary (PTO-413) Paper No(s). _____ .
2) Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) Notice of Informal Patent Application (PTO-152)
3) Information Disclosure Statement(s) (PTO-1449) Paper No(s) 8126103 6) Other:

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on November 15, 2004 has been entered.

Claim Rejections - 35 USC § 112 - Enablement

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3. Claims 35-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for detection of probes which comprise the pH or potential sensitive fluorophore attached to a steroid, to a head group of a sphingolipid or to the head group of a lipid have two 14 carbon chains which probes interact with a lipid bilayer, does not reasonably provide enablement for any pH- or potential sensitive fluorophore linked to a charged polymer without other structural information which interacts with any surface whatsoever. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman*. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The claims are drawn to a method of detection of binding of a species by detecting a fluorophore probe which interacts with the surface. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The breadth of the claims

The claims encompass a method of determination of the binding of a species to a surface, but the surface is not delimited in the claims and for claim 40, the fluorophore probe is not structurally delimited either. The claims read on any surface with a charge, whether the lipid bilayer shown in the specification or an air/water interface or into a polymer or into the surface of a piece of wood (which is a polymer of cellulose). Further, claim 40 reads on any probe with any structure whatsoever, so long as it encompasses a fluorescent probe. While the claims now are drawn to species with "electrostatic interactions" that occur with the polymer surface, this functional limitation

does not significantly address the breadth issues where nearly any polymer with charge and nearly any species falls within the scope of the claim.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant variability in the ability of compounds to be incorporated into surfaces. It would require significant and inventive experimentation to determine which groups, if any, could be attached to the fluorophore to stably incorporate the group at the surface of an air/water interface, the surface of a polymer, or the surface of a other compounds not specifically discussed or treated in the specification. Further, even with regard to the narrower embodiment of lipid bilayers, it would require significant experimentation to identify other stabilizing agents which could function other than those expressly listed in claim 19. With regard to the claim as currently drawn to any electrostatic interaction between a species and a polymer, this represents an immense amount of experimentation to determine which, if any, other polymers besides lipid bilayers would function to permit a change in fluorescent property and which, if any other fluorophores would function with these other polymeric surfaces.

The unpredictability of the art and the state of the prior art

The prior art of Zuidam teaches that the fluorophore can be incorporated into a membrane but the short carbon chain linked to the fluorophore was unable to stably interact with the surface. As Zuidam expressly notes "The liposomes containing DOTAP were unstable upon dilution (see page 45, column 2)." Zuidam further notes regarding liposomal complexes that "Fundamental knowledge is lacking and most of the achievements reached are based on trial and error (see page 44, column 1)."

Every single reference cited by Applicant in the IDS deals with biological membranes, which are lipid membranes. Thus, the broad nature of claim 40 is not supported by the prior art which suggests that it is unpredictable what elements are necessary for function in the species detection method. Further, the prior art of Gee, while teaching fluorophores, makes no suggestion of stable incorporation at surfaces.

The use of fluorophores on any surface for species detection is extremely unpredictable since it is unpredictable what effects the surface interactions will have on the fluorophore, it is unpredictable what elements are necessary to stabilize the fluorophore in a position near any surface and it is entirely unpredictable what elements of the fluorophore would function in a surface independent manner. For example, it is unpredictable what fluorophore would retain pH effect at an air/water interface, at an air/polymer interface or at an organic solvent/water interface. Even after identifying fluorophores, if any exist, which would function at these interfaces, the next step would be identifying components which would permit stable association of the fluorophores with the surfaces. This would require significant inventive chemical effort since each component would necessarily be specific for the fluorophore used and different fluorophores will have different chemical properties yielding different components necessary for stabilization.

Working Examples

The specification has a working example using hydroxycoumarin linked to dioleoyl phosphatidyl ethanolamine used in a lipid bilayer type surface, but there are no working examples using surfaces other than lipid bilayers or other fluorophores besides hydroxycoumarin or components for stabilization other than dioleoyl phosphatidyl ethanolamine.

Guidance in the Specification.

The specification, while suggesting the use of lipid bilayers and fluorophores generally and certain lipid based components for stabilization, did not teach the use of any other surface besides lipid bilayers and did not teach fluorophores and components which would function in any surface other than lipid bilayers.

In fact, the specification appears to contemplate only lipid bilayers. The specification states at page 7, lines 22-28,

"The surface may be, for example, the surface of a lipid vesicle (liposome), particularly a lipid vesicle comprising lipids having cationic head groups, such as are commonly used for DNA transfection. Alternatively, the surface may be a cell membrane. A lipid conjugated with a pH- or potential-sensitive fluorophore is incorporated into the liposome or other membrane bilayer; the level of incorporation is typically about 0.2 to 0.5 mole percent. The probes may also be incorporated into lipid monolayer structures, such as stable micelles and emulsion droplets, as well as other lipid phases, such as the cubic phase."

So there is no discussion of any other polymer surface besides lipid based polymeric surfaces in the specification whatsoever, which further supports the absence of enabled support for the broad claims that incorporate surfaces including any material whatsoever.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

In the instant case, as discussed above, the level of unpredictability and the teaching against the use of any surface and any stabilization component by the art is opposed to patentability (see Zuidam and Gee). The specification provides one with no

written description or guidance that leads one to a reliable method using any surface for detection. One of skill in the art cannot readily anticipate the effect of a change within the subject matter to which the claimed invention pertains. Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a single narrow working example and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 112 – Written Description

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 35-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register:

December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.)

Claims 35 and 37-42 encompass a genus of fluorophores whose fluorescence is dependent upon the binding or dissociation of a species at a surface. However, only three specific species of such fluorophores are even suggested by the specification, those linked to steroids, linked to sphingolipids or linked to lipids having at least two chains of 14 atoms. The genus includes variants for which no written description is provided in the specification including essentially any other chemical modification whatsoever. Thus, applicant has express possession of only three particular species, in a genus which is almost literally infinite and which clearly comprises hundreds of millions of different possibilities. Here, no common structural element or attributes of the genus of binding insensitive fluorophores are disclosed combined with the limitless numbers of charged polymers to which these fluorophores could be attached.

A second genus is that of surfaces. The only surface disclosed as functional is a lipid surface. However, the claims include any surface whatsoever. Not only is there no description of surfaces which are not lipid based, but the specification only discusses lipid surfaces, as exemplified at page 7, lines 22-28,

"The surface may be, for example, the surface of a lipid vesicle (liposome), particularly a lipid vesicle comprising lipids having cationic head groups, such as are commonly used for DNA transfection. Alternatively, the surface may be a cell membrane. A lipid conjugated with a pH- or potential-sensitive fluorophore is incorporated into the liposome or other membrane bilayer; the level of incorporation is typically about 0.2 to 0.5 mole percent. The probes may also be incorporated into lipid monolayer structures,

such as stable micelles and emulsion droplets, as well as other lipid phases, such as the cubic phase."

So there is no discussion of any other polymer surface besides lipid based polymeric surfaces in the specification whatsoever, which further supports the absence of written description for the broad claims that incorporate surfaces including any material whatsoever.

It is noted in the recently decided case The Regents of the University of California v. Eli Lilly and Co. 43 USPQ2d 1398 (Fed. Cir. 1997) decision by the CAFC that

"A definition by function, as we have previously indicated, does not suffice to define the genus because it is only an indication of what the gene does, rather than what it is. See Fiers, 984 F.2d at 1169- 71, 25 USPQ2d at 1605- 06 (discussing Amgen). It is only a definition of a useful result rather than a definition of what achieves that result. Many such genes may achieve that result. The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736 F.2d 1516, 1521, 222 USPQ 369, 372- 73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. "

In the current situation, the definition of the stable fluorophore and the definition of the surface with which the fluorophore can interact, lack any specific structure. This is precisely the situation of naming a type of material which is generally known to likely exist, but, except for the three named species of fluorophores and the single lipid based type surfaces, is in the absence of knowledge of the material composition of the components. This specification fails to provide descriptive support for the generic claim

to any fluorophore for a method where one is "observing a change in a fluorescent property ... upon binding or dissociation of a species" where the only change induced by the species is the change in pH or surface potential. This specification also fails to provide descriptive support for the use of the fluorophore on any surface.

It is noted that in Fiers v. Sugano (25 USPQ2d, 1601), the Fed. Cir. concluded that

"...if inventor is unable to envision detailed chemical structure of DNA sequence coding for specific protein, as well as method of obtaining it, then conception is not achieved until reduction to practice has occurred, that is, until after gene has been isolated...conception of any chemical substance, requires definition of that substance other than by its functional utility."

The current situation is a definition of the compound solely but its functional utility, as a stable fluorophore, or as a surface with which the fluorophore can interact, without any definition of the particular structural components required to achieve this function.

Also, in Vas-Cath Inc. v. Mahurkar (19 USPQ2d 1111, CAFC 1991), it was concluded that:

"...applicant must also convey, with reasonable clarity to those skilled in art, that applicant, as of filing date sought, was in possession of invention, with invention being, for purposes of "written description" inquiry, whatever is presently claimed."

In the application at the time of filing, there is no record or description which would demonstrate conception of any stable fluorophores other than those expressly disclosed which comprise the three species. Further, there is no description of any surfaces other than lipid based surfaces. Therefore, the claims fail to meet the written

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description requirement by encompassing compounds which are not described in the specification.

Claim Rejections - 35 USC § 112 – New Matter

6. Claim 41 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As MPEP 2163.06 notes “ If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. *In re Rasmussen* , 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).”

Here, claim 41 contains new matter, specifically the requirement that the surface is “not a lipid based surface”. A careful review by the examiner of the cited pages of the specification failed to identify any support for this new negative limitation. In fact, as noted by in the enablement rejection, page 7, lines 20-28, appear to indicate that “lipid surfaces” are preferred. As noted by MPEP 2173.05(I),

“ Any negative limitation or exclusionary proviso must have basis in the original disclosure. See *Ex parte Grasselli* , 231 USPQ 393 (Bd. App. 1983) aff'd mem., 738 F.2d 453 (Fed. Cir. 1984). The mere absence of a positive recitation is not basis for an exclusion. Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph as failing to comply with the written description requirement.”

Since no basis has been found to support the new claim limitation in the specification, the claim is rejected as incorporating new matter.

Allowable Subject Matter

7. Claims 19-33 are allowed.
8. The following is a statement of reasons for the indication of allowable subject matter: Claims 19-33 are now limited to lipid based surfaces with specific attachment motifs. As noted previously, there is no prior art which teaches the method now claimed. Also, the issue of enablement is overcome by the limitation of the claim to a lipid based surface, as opposed to the use of any surface.

Response to Arguments

9. Applicant's arguments filed November 15, 2004 have been fully considered but they are not persuasive.

Applicant argues that their citation of chapter 20 of a text entitled "Molecular Probes" provides detailed information regarding pH- or potential-sensitive fluorophores which can be used and that this overcomes the enablement and written description rejections.

First, with regard to the enablement rejection, a mere listing of probes referring the website <http://www.probes.com/handbook/sections/2004.html> does not address the issues raised in the Wands analysis given above. In particular, the website is postfiling date art dated November 6, 2004 (on December 7, 2004, the day viewed by the Examiner) which proves little about the state of the art prior to Applicant's filing date of February 2001 and effective filing date of February 10, 2000. Applicant's use of the "printer friendly" format lost the date of the update which they were viewing. As MPEP 2164.05(a) notes "Publications dated after the filing date providing information publicly

first disclosed after the filing date generally cannot be used to show what was known at the time of filing."

Second, the citation of the list of probes does not support any further enablement for the surfaces. In the cited website, no specific surfaces appear to be used at all. The citation does not address fluorophores which function in lipid bilayers or other surfaces. Therefore, the cited website cannot provide enablement even for the fluorophores because there is no evidence of record that any of the listed fluorophores would function in pH measurement when interacting with any surface whatsoever.

As noted previously, Plant Genetic Systems v. Dekalb (315 F.3d 1335 (Fed. Cir. 2003) shows that disclosure of only a single or limited number of species in an unpredictable area supports an enablement rejection. In that case, disclosure of only monocots did not provide enablement for dicots. The current situation is a similar attempt to obtain coverage over unpredictable elements which are less related than monocots and dicots. While both monocots and dicots are at least plants, the current case is drawn to any "oppositely charged polymer" and any surface. This claim is open not only to lipids shown in the specification, or the arabinogalactan-spermines and dextran-spermines further tested by Applicant, but encompasses a variety of biological polymers including DNA, RNA, many of the proteins currently in existence, a variety of cellulose polymers derived from trees and other plants, a variety of modified collagen polymers derived from extracellular matrix in mammals, and a myriad of other compounds. However, the claim is not even limited to this broad and nonenabled class of biological polymers but further encompasses any charged polymer whatsoever.

Given this immense scope for the claim, with literally hundreds of thousands or millions of different species, and only a single species enabled by the specification (and two additional related species shown in the arguments), it is entirely unpredictable whether polymers ranging from cellulose to polyethylene would operate in similar ways. Therefore, the conclusion that it would require undue experimentation to use other polymers for the analytical method is maintained.

Applicant then argues the written description rejection by cited the same website. As noted above, post filing date art does not provide descriptive support for an earlier filed invention. Also, Applicant also repeats the argument that the written description rejection should be overcome because the one of skill in the art would be readily able to determine, without undue experimentation, fluorophores which would function in the assay.

As noted previously, the issue with regard to description is not whether the method is enabled, though the enablement rejection above indicates the position of the office that the claims at issue, claims 35-42 are not, in fact, enabled, but rather whether Applicant had possession of the invention. This inquiry is not limited to cases involving genes, as shown by Gentry Gallery, in which the position of a console on a sectional sofa. In that case, the Court stated "In sum, the cases on which Gentry relies do not stand for the proposition that an applicant can broaden his claims to the extent that they are effectively bounded only by the prior art. Rather, they make clear that claims may be no broader than the supporting disclosure, and therefore that a narrow disclosure will limit claim breadth. " Similarly, in the current case, the disclosure is narrowly drawn to a

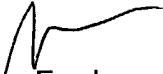
particular fluorophore. Only three species of fluorophores are taught in the specification and the entire specification and entire support revolve around the use of these three fluorophores in the lipid bases surfaces as claimed in allowed claim 19. The claims are drawn to a much broader class of fluorophores, whose nature and type are completely undisclosed and unknown by the specification. Therefore, the written description rejection will be maintained.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey Fredman whose telephone number is (571)272-0742. The examiner can normally be reached on 6:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571)272-0782. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Jeffrey Fredman
Primary Examiner
Art Unit 1637
12/3/09